MICHIGAN ENVIRONMENTAL SCIENCE BOARD

HYDROGEN SULFIDE PANEL MEETING SUMMARY
THURSDAY, DECEMBER 3, 1998
COURTYARD BY MARRIOTT
7799 CONFERENCE CENTER DRIVE
BRIGHTON, MICHIGAN

PANEL MEMBERS PRESENT
Dr. George T. Wolff
Dr. John A. Gracki
Dr. David T. Long
Mr. Keith G. Harrison, Executive Director

DEQ/OSEP SUPPORT STAFF PRESENT
Mr. Jesse Harrold, Environmental Officer
Ms. Patricia Hiner, Executive Secretary

I. CALL TO ORDER

Mr. Keith Harrison, Executive Director, called the Michigan Environmental Science Board (MESB) Hydrogen Sulfide Panel (Panel) meeting to order at 9:10 am.

II. EXECUTIVE DIRECTOR'S UPDATE

Mr. Harrison indicated that Panel chair, Dr. Larry Fischer, would not be able to attend the meeting. He provided a brief summary of the material that had been submitted to the Panel to date.

III. PRESENTATIONS

Ms. Maureen Barrett (AERO Engineering) reviewed the background of hydrogen sulfide (H_2S), stating that it was a ubiquitous compound with many natural sources. The U.S. Environmental Protection Agency (USEPA) has estimated the ambient concentration range to be 0.1 to 0.3 ppb. Natural sources, both land-based and aquatic, contribute approximately 90 percent of the total H_2S; 90 to 100 million tons. Varied anthropogenic sources also contribute to the total H_2S. These sources include feedlots, barns, pulp and paper production, rayon production, and the oil and gas industry. Additional sources are municipal and industrial water treatment and coal and oil combustion. The human body produces H_2S as well.

Many of the sources for H_2S have a potential for accidental, higher releases. The possible frequency and magnitude of these releases need to be taken into account in the development and implementation of ambient air standards. Naturally occurring ambient levels must also be determined. In Colorado, it was discovered that there were peaks in the one-minute values of 0.168 ppm adjacent to some of the natural hot springs.

Currently, many of the complaints regarding H_2S concern odors. Ms. Barrett stated that health-based issues and protection against negative health effects should be the focus of any regulatory process. Health effects data indicate that a large gap exists between levels of H_2S that would regulate odors and levels that would protect against adverse health effects. In general, nuisance odors occur in the ppb range while health-based thresholds are in the ppm range.

Odor threshold has been used as the basis for setting standards in some states. One of these states is California, which has a restricted one-hour standard of 0.03 ppm. California started with a 0.008 ppm, which is at the lower end of the odor threshold. This factor was then multiplied this by a factor of four, assuming that only part of the population would have difficulties from H_2S emissions. Minnesota uses the same level, but allows two exceedances per week. This reflects the state's experience in monitoring emissions. Texas set its standards of 0.12 ppm and 0.08 ppm (30 minute, industrial) based on the issue of odors.

The most restrictive standards are based on information from the USEPA's Integrated Risk Information System (IRIS). IRIS was used by the USEPA to establish chronic exposure criteria. The data used come from a study done on mice where the no observed adverse effects level (NOAEL) was found to be 30.5 ppm. In order to convert from a study period of six hours, five days a week to a sub-chronic exposure, a factor of 1.8 is applied. Then additional factors are applied for interspecies conversion, sub-chronic to chronic exposure, and general to sensitive subgroups. In addition, a factor of ten was added to cover uncertainty in the database. These factors result in a final value of 0.0007 ppm for chronic, lifetime exposure. However, in Colorado, where monitoring revealed frequent peaks over 0.1 ppm, natural background levels necessitated finding a different basis for standards.

Using acute health-based standards is an option employed by some states. Nebraska began with the National Institute of Safety and Health (NIOSH) value of ten ppm over ten minutes. It then took a safety factor of ten to account for sensitive subgroups, and set a standard of ten ppm over one minute. However, since Nebraska was using total reduced sulfur as a surrogate for H_2S, this standard has been challenged in court, and is not currently enforceable.

Other states used a value from the American Conference for Governmental Industrial Hygienists, Inc. (ACGIH). This value is also scaled, from an eight-hour daily exposure of ten ppm to a weekly exposure, and accounts for the sensitive sub-population. The resulting standard is 0.23 ppm for 24 hours, and is used by states such as North Carolina and Louisiana.

Among the groups that promulgate international and U.S. standards for industrial settings, NIOSH is generally more restrictive. For intermediate and chronic exposure, the USEPA value of 0.7 ppb is by far the most conservative. In comparison, the Agency for Toxic Substances and Disease Registry (ATSDR) has published a minimal

level of 0.5 ppm over one to 14 days. This is a reference concentration intended to minimize, or protect from, adverse health effects over a lifetime. Guidelines published by the World Health Organization include 0.11 ppm over a 24-hour period for H_2S.

Dr. Geoff Granville (Shell Canada, representing the American Petroleum Industry - API) indicated that there are many reviews of H_2S available, from the National Research Council study in 1979 to the ATSDR study in 1997. While there is much data, it is not always helpful. There is a consistent problem of trying to predict a NOAEL for various behavioral and neurological effects. Much of the information available is anecdotal rather than data from controlled exposure studies. There is a general consensus around some of the acute effect levels. Acute exposure to greater than 500 ppm results in central nervous system (CNS) toxicity, while acute exposure to greater than 200 ppm causes delayed respiratory toxicity and a one-hour exposure to greater than 20 ppm has a potential for eye irritation. While H_2S may be detectable within the range of less than one to ten ppb, there is a much uncertainty concerning the effects at these low levels.

Much of the acceptability of low-level H_2S exposure has to do with sociopolitical issues. Ambient standards for different regions vary by about 1,000-fold. This wide range is due to the perceived needs in different jurisdictions. This includes issues such as whether there should be nuisance or health-based standards, whether emission limits or ambient exposures should be the focus, and emergency situations versus normal operations.

The goal of the API research program is to minimize the uncertainty about toxicology at ambient levels. The API decided to focus on work done in 1979 on rodents by the Chemical Industry Institute of Toxicology (CIIT). The animals were exposed six hours a day, five days a week, to 10, 30, or 80 ppm H_2S. The report states that there were no effects other than body and brain weight decreases at 80 ppm.

Other information came from a sub-acute (five-day) study on behavioral effects and the neurochemistry involved. The same doses were used as in the earlier CIIT study and four end points were evaluated. First, after every exposure the fixed interval operate response was measured. This demonstrates neurological function by assessing the animal's ability to perform a task (pressing the correct lever) to receive a reward of food. Second, spacial awareness was tested after each exposure using the Morris maze. The other two evaluations were done after the final exposure. Motor activity was tested. Neurological effects could result in the activity level being either subdued or increased. The final thing done was to sacrifice the animal and dissect the brain, splitting it into five regions. The activity of neurotransmitters in the brain, in particular, catecholamines, was measured. No effects were observed in this study. Currently CIIT is doing additional work at higher doses, but the same results are being demonstrated.

A third study looked at sub-chronic reproductive and developmental neurotoxicity. Adult rats had at least 40 days of exposure to H_2S. After giving birth, females and their pups were exposed for five to 18 days. Males and non-pregnant females were exposed for

around 70 days. Reproductive performance was measured, as was growth and development of the pups. Tests included motor activity, passive avoidance, acoustics start, and the functional observation battery tests. There was nothing statistically significant found regarding any of the reproductive or neurodevelopmental/behavioral aspects. Pathological investigations did reveal damage of the nasal membranes at 80 ppm, as well as damage to the sensory nerve endings in the nose for smell. Ten ppm was definitely a NOAEL while there were possible slight differences at 30 ppm. Nasal damage, unless serious, is often reversible so there is debate about whether this should be considered an actual adverse effect.

Dr. Harvey Clewell (ICF Kaiser) stated that for about a year, he had been working with Jeff Gearhart and Mel Anderson on developing a physiologically-based pharmacokinetic model for H_2S. The purpose of this is to provide measures of tissue dose and using this information to extrapolate across different kinds of studies and end points. This would provide a consistent approach for risk assessment from dissimilar studies.

Risk assessment starts with toxicology data as it relates to effects. It assumes that there is an exposure that produces some effect. However, studies may use differing exposure parameters such as acute, intermittent, or continuous. The effects may be demonstrated in humans, or they may be seen in animals such as rats or pigs. In the case of H_2S, the exposure of interest is long-term and continuous. Unfortunately, there are no studies that measure precisely that type of exposure. In order to extrapolate information from a different type of study, some type of tissue dose is measured at the site where interaction of the chemical with the target tissue is producing the observed effects. Measuring the effects of inhaled H_2S, involves measuring the concentration of sulfide ions, the form of sulfur found in the body. One of the effects of the sulfide ion, whether inhaled or endogenously produced, is to inhibit sulfide oxidase. Since this is a known interaction, it is possible to obtain quantitative information on that during an exposure.

A model needs to be developed to relate the pharmacokinetic studies to the toxicology studies. This model would provide different routes of exposure and important target tissues, incorporating metabolism and elimination in order to be able to describe the pharmacokinetics and delivery of H_2S to the target tissue. The model can be used for short or long-term studies, correlating the observed toxic effects in the original toxicology studies with specific measures of the levels found in target tissues. Extrapolation can then be done to the exposure of concern, chronic continuous exposure.

Toxic effects of concern for H_2S include CNS and developmental and respiratory effects. Risk assessment considerations include determining which effects will be the limiting, or critical, effects. In addition, different effects could be critical depending on the exposed population or duration of exposures, etc.

The physiologically based, pharmacokinetic (PBPK) model was developed to measure

acute CNS effects from H_2S. It is now being extended to also apply to the chronic exposure situation. This model examines the course of the toxic compound in question as it is inhaled in the air into the lungs, crosses into the plasma in the alveolar region and then flows in the blood to the other tissues in the body. Tissues with similar kinetic properties are grouped together. The model considers factors such as intravenous and oral exposure, as well as metabolism in the liver and binding in red blood cells.

To run this model, a continuous simulation line was used. This is a model used often by chemical engineers. It has now been written to support physiological applications. In order to construct a physiological model, the literature must be reviewed to determine what data are available. Kinetic studies on H_2S are limited for PBPK model validation. Most were motivated by the high concentration, acute problem, and were short-term studies that examined exposure to very high (lethal) doses.

One study examined mice that were exposed to 400 ppm H_2S for an hour, after which the animals were sacrificed and samples were taken for evaluation. One question that this study attempted to answer was how long the H_2S stayed in the body after an exposure. The varied sulfide levels in the animals' blood reflect the speed at which H_2S leaves the blood and is related to the variation in sample collection times. Although this results in data that may not be precise, what the model predicts is that there is a rapidly rising steady state and a very rapid clearance at the end of the inhalation exposure. This would infer that blood concentration is directly related to ambient air concentration.

Other studies have looked at oral ingestion of hydrogen sodium sulfide and other salts and looked at the distribution in the body, as well as the production of metabolites. Sodium sulfide has been administered intraperitoneally with the resulting metabolite, sulfate, measured in the urine. Intravenous administration has also been done, but is difficult to model due to the sudden onset of high concentrations. There is variation and uncertainty in the data from all these studies. The studies that CIIT will be doing are inhalation studies where it will attempt precise measurements of different sulfide species, not only in the blood, but in specific tissues. These studies will expose animals to a range of concentrations and will measure the time course for H_2S, as well as sulfite and sulfate in multiple tissues. CIIT will also be measuring the time course for inhibition of cytochrome oxidase in the brain, heart and liver. This is a well known and important interaction of sulfite with the tissues.

The PBPK model can bring together diverse data from different exposures. The current model includes four routes of exposure, inhalation, oral, intravenous and intraperitoneal. It includes information on sulfide blood time course, urinary sulfate excretion, blood sulfate concentrations, and uses a simple metabolic scheme of converting sulfide directly to sulfate. After the initial data collection to develop the model, CIIT will gather additional data to validate different types and durations of exposure. There will also be information collected on the binding of sulfite in different tissues and in red blood cells. This will help to predict the time course as a function of dose.

These biological processes are described using rate equations that subtract the amount of H_2S metabolized and the amount that leaves from that which enters the body.

Binding equations demonstrate the total H_2S in tissue as that which is partitioned and that which is bound to cytochrome oxidase. Previous studies have examined the recovery of cytochrome oxidase from inhibition; however, the data are not very precise. The CIIT studies will be looking at lower exposures and less inhibition, in order to measure the time course of the release of inhibition.

The other area of current model development is nasal effects. This takes a different approach as there is direct diffusion, rather than a systemic delivery of material mediated by the blood. The model includes various elements of nasal anatomy, with similar models available for acrylic acid, vinyl acetate and methylmethacrylate. These models predict the accumulation of the compound in different areas of the nose. Data being collected by CIIT will show the concentrations of the sulfur species in different nasal regions, as well as looking for evidence of irritation and other tissue responses.

The goal is to be able to organize the data quantitatively and identify critical data gaps, particularly for extrapolation to chronic exposure. This should allow for extrapolation to humans with a clear definition of the disposition or elimination of H_2S and its metabolites.

Dr. Geoff Granville commented on how uncertainty is used. He stated that the USEPA often used a 100-fold safety factor in the extrapolation of the effects on a rat to those on a human being. This is highly conservative, and the PBPK model could give better information to make decisions.

He indicated that a preliminary conclusion from the API research was that there was no obvious neurological behavioral toxicity from H_2S at 80 ppm. It is unlikely that ambient levels less than one ppm are harmful, and susceptibility at low doses (10-100 ppb) does not seem important. The PBPK model will help with interspecies extrapolation.

Therefore, concerns regarding the acceptability of H_2S in the low dose (less than one ppm) range are more driven by behavioral issues, such as the impact of odors and the resulting quality of life. The API is not aware of any concerns with H_2S regarding cancer or mutations. Also, all the occupational effects of H_2S are rapidly reversible, so that there is no evidence of accumulation of injury over the working lifetime.

The question for Michigan is upon what criteria should the ambient air standard for H_2S be based? H_2S is one of a number of gases with unacceptable organoleptic properties, so this is a general policy issue. Should the standard protect against nuisance or against actual health effects? Are the emissions controlled for both emergencies and normal daily operations? The API data indicate human health effects are unlikely at ambient levels below one ppm. However, exposure to one ppm H_2S over long periods of time could produce health effects by a negative impact on the quality of life. Adding a safety factor of ten would be appropriate. In addition, another factor of ten could be added to protect susceptible individuals.

IV. PANEL DISCUSSION

Dr. Long asked whether the basis for the challenge to the Nebraska regulations was the switch from a one-minute standard of ten ppm to an instantaneous value of five ppm.

Ms. Barrett answered that ten ppm/one-minute had been the standard proposed by the toxicologist. Then the focus had shifted from science to politics and the regulation had been set at five ppm/instantaneous. It was also questioned in the challenge whether an instantaneous measurement was feasible.

Mr. Harrison asked whether the ambient air quality study done in Colorado had ever been replicated. Ms. Barrett replied that it was an extensive study, with eight or nine sites set up which operated over six to eight weeks. Most of these sites had a number of monitors set up. The results were correlated with weather conditions, and there were very defined quality assurance procedures. However, it was a one-time study that has not been replicated.

Dr. Long questioned the type of equations developed for extrapolation from animal to human exposure. Dr. Clewell responded that there are physiological parameters already in place, based on work with other chemicals. Some data are attainable *in vitro*, such as determining that the inhibition of cytochrome oxidase has the same concentration relationship in humans and in the animal studies. To validate the model for humans, less invasive procedures such as nasal lavage can be performed.

Dr. Long asked whether it was possible to use low-level exposure and monitor sulfate emissions. Dr. Clewell answered that it might be possible, depending on the other sources of exposure for a population.

Dr. Long also asked Dr. Clewell how the preliminary results of his work in extrapolating animal to human exposures compared to that done by the USEPA. Dr. Clewell said that the USEPA response to uncertainty was strongly conservative. It assumes that the entire intake of chemical in the airflow is deposited in the surface area of the region of concern. However, diffusion into tissue is dependent on factors such as the amount of surface area available. The USEPA also adds a factor of seven to nine, considering humans to be more sensitive, which they are probably not. At ten ppm for ten minutes, the concentration is roughly the same for a rat or for a human.

Dr. Long expressed concern about going from a 40-day exposure to making an annual exposure estimate. He questioned whether the reversibility of H_2S damage, such as that to the cytochrome oxidase system, was compromised after chronic exposure. Dr. Granville stated that this was often an area of concern for people, and that this was one reason for including a safety factor. A 90-day study has been done. This is one-eighth of a rat's lifetime. Also, there are many people with lifetime exposures of one-half ppm who show no effects. This includes hog farmers and some of the residents of Colorado or New Zealand. Dr. Clewell added that USEPA studies in Cincinnati used a factor of ten in going from sub-chronic to chronic endpoints. This is similar to going from one-eighth to a full lifetime exposure.

Dr. Gracki asked what was the minimum cost for readily available commercial instruments for monitoring. Ms. Barrett stated that for about $10,000, a Jerome Monitor can be obtained, which will go down to the ppm range. It can be set up for short-term fixed locations, but needs some type of shelter. Ms. Barrett also said that the compilation of the survey that they had done was in booklet form, which she would

distribute to the Panel. Dr. Clewell added that ATSDR was scheduled early next year to publish an updated version of the toxic profile for H_2S.

Dr. Wolff questioned whether the Panel would have access to the CIIT report. Dr. Granville stated that the public review of the five-day report is right now. The more involved study should be ready within the next few weeks. API would be willing to send it directly to the MESB.

V. PUBLIC COMMENT

Mr. Bill Myler (Michigan Oil and Gas Association) stated that in his industry, under normal conditions, there were spikes in the levels of H_2S. He asked for clarification on this exposure issue, and what level should be allowed for a ten or 30-minute period, assuming there were no adverse health effects. Dr. Granville responded that there was no direct answer, and that this is where individual susceptibilities could become important. There are published acute exposure guideline levels that have been used by the National Academy of Science. There are values for 30-minute to four hour exposures at levels that should produce no effects, mild effects, and serious effects in people. The USEPA and other groups have produced similar numbers. For instance, 1.7 ppm for one hour was considered a level that would produce no effects. For 30 minutes, it was two ppm. Fifty ppm for one hour is the value that is likely to produce serious effects. Evacuation guidelines use 20 ppm as the level at which evacuation of people is mandated.

VI. PANEL ASSIGNMENTS

Mr. Harrison restated the assignments that had previously been given to the Panel members. Dr. Wolff would provide an overview of the sources of H_2S, would work on the nature of H_2S and the sensitivity limits, Dr. Long would be provide information on the monitoring of exposure to H_2S in Michigan, and Dr. Fischer would write on the effects in the body; the toxicity of H2S, both acute and chronic. Mr. Harrison indicated that he would provide the introductory material and put the report together.

VII. NEXT MEETING DATE

No additional meetings were scheduled.

VIII. ADJOURNMENT

The meeting was adjourned at 11:26 a.m.

Respectfully submitted,
Keith G. Harrison, M.A., R.S., Cert. Ecol.
Executive Director
Michigan Environmental Science Board